1033-35 Hemorrhage Incidence with Low Molecular Weight Heparin vs Unfractionated Heparin in Patients with Unstable Angina or Non-Q-wave Myocardial Infarction

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Studies of enoxaparin, a low molecular weight heparin (LMWH), and unfractionated heparin (UH) in deep vein thrombosis treatment show comparable rates of hemorrhage in both groups. A large study in orthopedic surgery showed no heparin induced thrombocytopenia (HIT) in the LMWH (enoxaparin) group compared to the UH group. The ESSENCE study was a randomized, double-blind, placebo-controlled study of 3172 patients comparing enoxaparin 1 mg/kg sc bid vs adjusted-dose UH via continuous IV infusion. Patients within 24 hours of onset of acute myocardial ischemia were eligible and trial therapy was administered for a minimum of 48 hours to a maximum of eight days. The predefined primary safety endpoints of major hemorrhage (hemorrhage associated with a > 3 gm/dl Hg drop or ≥ 2 unit PRBC transfusion), minor hemorrhage, and the incidence of possible HIT were analyzed. *Results:* The mean duration of therapy was 3.2 days. The overall rates of hemorrhage for the index hospitalization were: major hemorrhage 7%, minor hemorrhage 10%. Sixty-eight percent of major hemorrhages occurred after discontinuation of study therapy in the setting of CABG. Overall rate of possible HIT: 0.3%. The incidence of primary safety endpoints in the LMWH vs UH treatment groups will be presented.

1033-36 Evaluation of the Predictive Performance of a Multi-Demographic Based Heparin Dosing Protocol in Acute Coronary Syndromes

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Recent literature supports the concept that achieving a therapeutic APTT with heparin can improve patient outcome in patients with unstable angina (USA) and acute myocardial infarction (AMI). Dosing heparin via a weight-based protocol has become the standard of practice, but weight accounts for only approximately 30% ($r^2 = 0.30$) of the variance of the heparin dose. We hypothesized that other patient specific variables may be predictive of heparin dosing requirements, and that integration of these variables into a dosing protocol would further optimize anticoagulation with heparin in USA and AMI. A retrospective chart analysis on 140 patients with the diagnosis of USA or AMI and treated with IV heparin was conducted. Multiple regression analysis identified height, total body weight, age, gender and diagnosis (AMI or USA) as being predictive of heparin requirements. ($r^2 = 0.47$). A dosing nomogram was developed and implemented in November, 1995. Performance of the nomogram was evaluated over a 6-month period and compared to the original 140 patient data set. Interim analysis (n = 102) showed the nomogram significantly improved the percentage of patients with a therapeutic APTT (60–85 seconds) within 24 hours from 40% to 91% ($p < 0.001$). There were no major bleeding episodes. *Conclusion:* The use of a multi-demographic based heparin dosing protocol significantly improved heparin therapy in patients with acute coronary syndromes. The comparison of the multi-demographic nomogram vs. a standard weight-based protocol seems justified at this time.

1033-37 Is There A Role For IV Heparin in Unstable Angina Patients Prior to PTCA?

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The optimal timing of PTCA in unstable angina (USA) pts is controversial. Early reports suggested that the risk of PTCA may be decreased in pts who have been stabilized with aspirin and IV heparin for several days. However these studies were limited by the fact that medically refractory USA was likely reason for earlier PTCA, and more critically ill pts are known to have a higher event rate. The purpose of this study was to evaluate whether delaying the PTCA in order to stabilize the plaque affected the outcome. We reviewed the hospital course of all pts admitted over one year period with USA whose symptoms were severe enough to require emergency room evaluation and admission to rule out MI, and required PTCA during the index hospitalization. Of the 305 pts, 166 pts received < 48 hrs (Group I) and 139 pts received > 48 hrs (Group II) of IV heparin before PTCA. Both the groups were well matched. The procedural success was similar in both the groups (98% vs 97% p = 0.72). The complication rate was similar in both the groups including abrupt closure (1% vs 3%), emergency CABG (1.8% vs 0.7%), CK leak (4% vs 2%), Non Q MI (3% vs 2.8%), Q wave MI (0.6% vs 0) and death (0.6% vs 0.7%). Length of the hospital stay was significantly prolonged in Group II. On multivariable analysis, the no. of diseased vessels and presenting ECG were predictive of events but not the duration of heparin infusion. *Conclusion:* In USA pts. undergoing PTCA, IV heparin infusion did not influence the procedural outcome or post-procedural complications, but prolongs the hospital stay. These data suggest that early PTCA of USA pts is safe and may be cost effective.

1033-38 Combining IIb/IIIa Inhibition and Heparin for Acute Coronary Syndromes: Evidence of a Gradient for Bleeding Hazard from the PARAGON Randomized Factorially Designed Trial

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Combining potent antiplatelet with heparin therapy for acute coronary syndromes may improve clinical outcomes. The risk of increased serious bleeding is unknown. PARAGON A enrolled 2282 pts with unstable angina/non-Q MI in a multicenter, international randomized trial of 2 doses (1 or 5 μq/min) of lamifiban (LL and HL), a nonpeptide platelet glycoprotein IIb/IIIa inhibitor, with or without heparin (H), versus H and aspirin. Bleeding was classified as intermediate (IB) when a blood transfusion was required or the Hgb dropped > 5 g/dl without hemodynamic instability and as major (MB) when hemodynamic instability occurred. Bleeding outcomes by treatment follow:

	LL, H (n = 377)	LL, noH (n = 378)	HL, H (n = 373)	HL, noH (n = 396)	H (n = 758)
IB	6.6%	4.8%	10.5%	8.3%	4.8%
MB	0.5%	0.8%	2.4%	1.5%	0.8%
Transfusions	6.1%	4.0%	8.9%	8.9%	4.7%
Hem. CVA	0.3%	0.3%	0.0	0.0	0.0

In this first randomized trial of GP IIb/IIIa inhibition with and without H, there is a definite incremental gradient of bleeding hazard. Combination therapy with H and HL appears especially problematic. Therapeutic strategies combining both types of antithrombotic therapy need to consider this incremental risk.

1033-39 Endpoint Adjudication by a Clinical Events Committee Can Impact the Statistical Outcome of a Clinical Trial: Results From GUSTO-IIb

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A blinded centralized Clinical Events Committee (CEC) review process was used to adjudicate suspected reinfarction endpoints in the GUSTO-IIb trial in which 12,142 patients with acute coronary syndromes were randomized to heparin or desirudin. We compared the primary endpoint (30-day death or reinfarction) as reported on the Case Report Form (CRF) with that reported by the CEC:

	Desirudin	Heparin	P-value
CRF	8.4%	9.6%	0.016
CEC	8.9%	9.8%	0.058

Although more patients were identified as having reinfarctions by the CEC process, the CEC data showed a 3.3% lower relative risk reduction of the primary endpoint compared with the CRF data and the statistical significance was less. There were 359 reinfarctions about which the site and the CEC disagreed. Patients identified on the CRF but not by the CEC more often had chest pain and had higher median CPK values (744 vs. 629, p = 0.21).

Primary endpoint event rates determined by the CEC or the site investigator were only modestly different but the perceived effect on the overall p-value was substantial. Whether this is due to random chance or a difference in identification and adjudication of suspected events by the systematic review process used by the CEC is not known, but are important implications for future clinical trials.